A theoretical analysis of the conformational behaviour of substituted methylenecyclohexanes

Robert C. Mawhinney, Heidi M. Muchall, and Jean Lessard

Abstract: The use of the PBE0 hybrid density functional theory method in conjunction with the COSMO solvation model allowed us to reproduce, both qualitatively and quantitatively, the experimentally observed conformational compositions of 2-substituted and 2,7-disubstituted methylenecyclohexanes. An analysis revealed several different interactions that influence the overall equilibrium. It was found that the endo (general) anomeric effect plays a significant role in the equilibrium and that the “unsaturation effect” possibly comprises two effects.

Key words: conformational analysis, methylenecyclohexanes, anomeric effect, unsaturation effect.

Résumé : L’utilisation de la méthode théorique fonctionnelle de densité hybride PBE0 de concert avec le modèle de solvation COSMO nous permet de reproduire qualitativement et quantitativement, les compositions conformationnelles, observées expérimentalement, des méthyléne cyclohexanes substituées en position 2 et disubstitués en positions 2 et 7. Une analyse révèle plusieurs interactions différentes qui influencent l’équilibre global. On a trouvé que l’effet anomère endo (général) joue un rôle important dans l’équilibre et que l’effet d’insaturation comporte probablement deux effets.

Mots clés : analyse conformationnelle, méthyléncyclohexanes, effet anomère, effet d’insaturation.

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Introduction

The anomeric effect is invoked to explain the unusual stability of the more sterically unfavoured synclinal (gauche) conformer over the sterically favoured antiperiplanar (anti) conformer (1). A number of theories have been hypothesized to explain these findings (2). To test these theories, Lessard and co-workers (3–6) assessed the equilibrium composition of a number of systems using 13C NMR spectroscopy, including substituted methylenecyclohexanes.

The first article in the series (3) revealed that the dipole–dipole – dipole–quadrupole and rabbit-ear (or n–n interaction) theories for the anomeric effect were negligible (the latter because the chosen system did not have any endocyclic atoms with electron lone pairs), leaving only the double bond – no bond resonance or σ∗\text{C}=\text{O} orbital overlap as the main interaction. This appeared to explain the finding that the introduction of a methoxy substituent to the methylene group (position 7) in 2-methoxymethylenecyclohexane led to a stabilization of the axial conformer to such an extent that the equatorial conformer was not observed.

In the second paper (4) this was explored further by changing the 2-substituent. It was found that the introduction of a π system had the unexpected result of switching the conformational preference from axial to equatorial, with the proportion of equatorial orientation on going from methoxy (OMe) to vinyloxy (OVi) to acetoxy (OAc) increasing from 41% to 61% to 80% at 0 °C. Based on double bond – no bond resonance, the increase in anion stability of the 2-substituent along this series should produce the opposite effect. Similarly, the π\text{C}=\text{O} interaction should become more pronounced, since the σ∗\text{C}=\text{O} orbital energy should decrease along the series. This counter observation was termed the “unsaturation effect”.

In the last paper of this series (6), the authors brought together all previous results, as well as those for several similar systems, and concluded that the generalized anomeric effect is operating in these systems along with a contribution from electrostatic (dipole–quadrupole) interactions. Most important, however, is the as yet unexplained “unsaturation effect”, which appears to override the generalized anomeric effect in a number of cases.

To understand the “unsaturation effect”, we started a computational study of the axial preference for the 2-substituted...
methylenecyclohexanes (7). The experimentally observed trend was reproduced qualitatively. While the equilibria for the methoxy- and vinyloxy-substituted compounds were best obtained at single point solvated levels of theory, the large equatorial preference for the acetoxy species could only be reproduced when solvent-optimized geometries and energies were employed. Even then the equilibrium composition could only be estimated, since a minimum for one of the conformers was not located.

In this paper we have undertaken a reexamination of the 2-substituted equilibrium compositions. We report that the use of the COSMO solvation model (8–10) in conjunction with the empirical-parameter-free PBE0 hybrid density functional method (11, 12) not only correctly predicts the compositional preferences in the 2-substituted methylenecyclohexanes but also those seen for the 2,7-disubstituted systems (Scheme 1). This combination of theory and solvation model has recently been shown to give reliable results for examining the role of stereoelectronic effects in the collagen dipeptide (13).

Computational details

The Gaussian 98 suite of programs was used in all calculations (14). The minimum energy conformations were optimized using the empirical-parameter-free hybrid density functional PBE0 (11, 12) and the Pople split valence 6-31G(d) basis set (15–19), starting from the previously optimized gas phase HF/6-31G(d) structures (7). The COSMO polarizable continuum solvent model (8–10) was used, with dichloromethane as solvent, in all optimizations. All minima were confirmed by harmonic vibrational frequency analyses. Since all relative energies are based on rotational conformers, there is negligible dependence on entropy, and we report zero-point corrected, as opposed to free energy, values.

Results and discussion

As in the previous work (7), rotational isomers for both the axial and equatorial conformers were explored. In all cases, two rotamers are obtained within a 2.5 kcal/mol cut-off criterion. In Fig. 1 the structures for 2-OMe are given. As one can see, the C—R bond is aligned antiperiplanar with one of two possible C—C bonds, either C—C or C—C(sp)

This general feature is the same in all systems. All species will from here on be labelled by their conformations, axial (a) or equatorial (e), antiperiplanar to C(sp) or C(sp)

(i.e., a(sp3), a(sp2), e(sp3), e(sp2)), as shown in Fig. 1. In the case of the vinyloxy-substituted system there are twice as many conformers because of the cis and trans orientations in the C=CH2 fragment. While also possible for the acetoxy substituent, it was found earlier (7) that the cis species lie around 8 kcal/mol higher in energy and therefore are not a factor in the equilibrium composition. Unlike the previous study, we have now been able to locate solvent-optimized minima for all four conformers in the acetoxy system and can therefore concentrate on understanding the causes of the effects that lead to the observed equilibria.

Compositional analysis

The experimentally observed axial:equatorial equilibrium composition for the 2-substituted methylenecyclohexanes is

59:41 (2-OMe), 39:61 (2-OVi), and 20:80 (2-OAc) (4) and for the 7-substituted 2-methoxymethylenecyclohexane systems is 12:88 (7-CN), 95:5 (7-OMe), and 88:12 (7-Ph) (5). The relative energy differences for each of the species that make up the equilibrium are given in Table 1. The equilibrium composition is derived from these energy differences by combining the Boltzmann distribution relationship with the molar fractions distribution relationship (20, 21). As shown in Table 1, our results are both qualitatively and quantitatively in good agreement with the experimental values. The largest differences are observed for 2-OVi (Δ = −12%) and 7-Ph (Δ = +16%). All other results are within at

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Table 1. Relative energies and equilibrium compositions (evaluated at experimental temperatures).

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<tr>
<th></th>
<th>2-OMe&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2-OVi (trans)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>2-OVi (cis)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>2-OAc&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>ΔE (kcal/mol)</td>
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<td>a(sp&lt;sup&gt;3&lt;/sup&gt;)</td>
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<td>0.00&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>29.3</td>
<td>23.5</td>
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<td>&gt;95</td>
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<sup>a</sup>Relative energies include zero-point vibrational corrections.

<sup>b</sup>Equilibrium composition evaluated at 0 °C.

<sup>c</sup>Equilibrium composition evaluated at -113 °C.

<sup>d</sup>Total energies (in hartree (1 hartree = 4.3597482 × 10<sup>-18</sup> J) for the lowest energy conformers: -387.813339 (2-OMe), -425.849143 (2-OVi), -501.049114 (2-OAc), -479.96288 (7-CN), -502.179296 (7-OMe), -518.517203 (7-Ph).

The operation of another effect, the exo-anomeric effect, is revealed by the <i>r<sub>C-O</sub></i> entries in Table 2. When O–R<sup>1</sup> is antiperiplanar to <i>C<sub>2</sub></i><sup>+</sup> (left hand structures in Fig. 1), the overlap between an oxygen lone pair (π<sub>O</sub>) and σ<sub>C<sub>2</sub>C<sub>2</sub></sub> is maximized. Consequently, <i>r<sub>C-O</sub></i> is found to be longer in 2-OMe<sup>a</sup> and e(sp<sup>3</sup>) than in a(sp<sup>3</sup>) and e(sp<sup>2</sup>) (Table 2). Simi-
larly, when O–R \(^1\) is antiperiplanar to C\(_{sp^2}\) (right hand structures in Fig. 1), the \(n_\text{O}–\sigma_{C-C\text{sp}^3}\) interaction is maximized and \(r_{C-C\text{sp}^3}\) is longer in these species. These results also demonstrate that the effect on distance is larger in C—C\(_{sp^2}\) than in C—C\(_{sp^3}\). For example, in the 2-OMe case the former changes by 0.006–0.007 Å and the latter by 0.004 Å. This is a reflection of the differing strengths of the C\(_{sp^3}\)—C\(_{sp^2}\) and C\(_{sp^2}\)—C\(_{sp^3}\) bonds, as shown by the shorter overall C—C distances.

As expected, this effect diminishes as O–R \(^1\) becomes more electronegative. The average \(r_{C-C\text{sp}^3}\) bond difference decreases from 0.004 Å (2-OMe) to 0.003 Å (2-OVi) and to 0.002 Å (2-OAc). Similarly, the average \(r_{C-C\text{sp}^2}\) bond difference decreases from 0.007 Å (2-OMe) to -0.004 Å (2-OVi) and -0.003 Å (2-OAc). In the \(r_{C-C\text{sp}^3}\) case, there is virtually no variation in the axial and equatorial differences. The \(r_{C-C\text{sp}^2}\) case, on the other hand, exhibits some variation between the axial and equatorial differences, which also increases along the series 2-OMe, 2-OVi, and 2-OAc.

The effect of 7-substitution is rather small, if present at all, and no discernible pattern can be ascertained in the \(r_{C-C\text{sp}^3}\) case. The \(r_{C-C\text{sp}^2}\) bond distances reveal that the addition of an electron withdrawing group increases the \(sp^3–sp^2\) difference in both anomers (7-CN), an electron donating group decreases it in the axial anomer (7-OMe), and conjugation increases it in the equatorial anomer (7-Ph).

Aside from the changes due to 7-substitution, the C=C distance is fairly insensitive, owing to the stiffness of the bond (even more so than for the C\(_{sp^2}\)—C\(_{sp^3}\) bond). This is expected, and the lack of any appreciable change in C=C distance on its own does not imply that \(n_\text{O}–\pi_{C-C}\) and \(n_\text{O}–\sigma_{C-C}^\pi\) interactions do not play a significant role in these systems, as has been concluded earlier (3, 5). In fact, the expected small lengthening of the C=C bond in the axial species can be seen most clearly in 7-OMe and 7-Ph.

### Decomposition of energy differences

The equilibrium composition depends on the energy differences between the different species, as described earlier. As well, the Edward–Lemieux effect (which incorporates both the endo- and exo-anomeric effects, similar to our case) can be “energetically quantified by the energy difference between the sum of the endo- and exo-anomeric effects for one of the anomers and the sum for the other anomer” (22). Within this context, we have plotted the energy relationships between the different conformers (the \(cis\) and \(trans\) components of vinyloxy have been separated) as a function of the \% axial composition (all calculated at 0 °C). The overall results, along with the linear trend lines and corresponding correlation coefficients, are presented in Fig. 2.

In most cases there does not seem to be any direct relationship between energy difference and equilibrium composition. The one exception is the \(e(sp^3) - a(sp^3)\) energy difference, where there is a strong correlation \((r^2 = 0.97)\). This relationship corresponds to the endo- (generalized) anomeric effect, as Lessard and co-workers have concluded (6). However, our results do not show a second overall effect offsetting it; perhaps there are two effects within the subsets that are masking each other on a global scale. To explore this further, we have separated out the two systems, 2-OMe, 2-OVi(\(cis\)), 2-OVi(\(trans\)), and 2-OAc (“2-substituted”) and 2-OMe, 7-CN, 7-OMe, and 7-Ph (“7-substituted”) and again plotted the energy differences between the different conformers as a function of the \% axial composition. These are given in Figs. 3 and 4, respectively.
The $e(sp^3) - a(sp^3)$ energy difference shows the same strong correlation ($r^2 = 0.97$ and 0.96) in both 2- and 7-substituted systems. In the 2-substituted systems there is also a considerable correlation ($r^2 = 0.90$) with the exo-anomeric effect in the axial conformers, $a(sp^2) - a(sp^3)$, as seen in Fig. 3. The 7-substituted systems, where the
substituent effect is removed from the exo portion of the ring, do not show any correlation ($r^2 = 0.19$) with the $a(sp^2) - a(sp^3)$ energy difference. They do, however, exhibit a strong correlation ($r^2 = 0.98$) with the other endo-anomeric effect, $e(sp^2) - a(sp^3)$ (Fig. 4).

The fact that there are two main trends to each series and only one of them in common suggests that the “unsaturation effect” is a combined effect. There is no straightforward explanation, and since within each conformer there are three common energy components (steric, electrostatic, and electronic) (23), a full understanding will only come from a complete analysis of all energetic contributions. Also, one must realize that most of the data points in the figures are essentially clustered at one end, as intermediate experimental data are not available at this moment. Further studies, both experimental and computational, are planned to remedy this situation.

Conclusions

In this work we have shown that the combination of PBE0 and COSMO reliably predicts the experimentally observed axial:equatorial equilibrium compositions in 2-substituted and 2,7-disubstituted methylenecyclohexanes. We have analyzed the compositions with respect to both the endo- and exo-anomeric effects, jointly known as the Edward–Lemieux effect.

The geometries of the species that make up the equilibrium composition revealed evidence of three different effects. The $r_{C-O}$ distances exhibit the generalized anomeric effect. The exo-anomeric effect reveals itself as an increase in $C-C$ bond lengths due to $n_O-\pi^*_{C=C}$ interactions. The rigidity of the $C=C$ bond limits its use as a detector of $\pi_{C=C}-\sigma_{C,O}$ and $n_O-\pi_{C-C}$ interactions. However, 7-substitution has an effect on $r_{C-O}$ in both anomers, unlike typical anomeric systems, which implies that the methylene $\pi$ system might be the source of the “unsaturation effect”. This is supported by an analysis of energy differences and their relationship to the observed equilibrium composition in that an overall endo- (generalized) anomeric effect for one of the rotamers ($e(sp^3)-a(sp^3)$) is accompanied by two more correlations within the subsets of 2- and 7-substituted systems.

Studies are now underway to examine this further. These include an AIM analysis (24) of the electron density, as has been done previously (25–27); an NBO analysis (28) to examine the role of the suspected orbital interactions (29–34); and a bond energy analysis (35–37), which, to our knowledge, has never been used for the examination of the anomeric effect but should reveal results about steric, electrostatic, and electronic effects similar to other energy decomposition methods (38–40). As well, experiments are underway to examine all possible permutations within the two subsets.

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